Kansas Medical Assistance Program

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GABAPENTIN (Neurontin®)

Evidence for Off-Label Use

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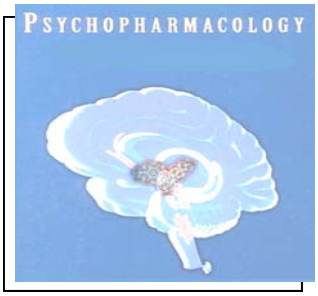

In December of 1993, gabapentin (Neurontin®) was approved by the U.S. Food and Drug Administration (FDA) for adjunctive therapy in the treatment of partial seizures in patients over the age of 12 years.[1] Since then, it has gained widespread use with significant utilization for non-FDA approved indications. In 2000 the partial seizure indication was expanded to include children age 3 to 12. It gained FDA approval for postherpetic neuralgia in adults in 2004 (see Table 1). However, published reports and small studies describe its use in a variety of medical disorders, including diabetic neuropathy, acute pain, migraine, trigeminal neuralgia, bipolar disorder, and anxiety disorders. Some of these uses have proven legitimate via controlled clinical trials, while others have not fulfilled their early apparent promise.[2,3] This newsletter will review the most pertinent clinical data available on the various off-label uses of gabapentin.

Table 1: FDA-Approved Gabapentin Indications[1]

- Adjunctive therapy in the treatment of partial seizures with or without secondary generalization in patients over 12 years of age with epilepsy
- Adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 to 12 years
- Management of postherpetic neuralgia in adults

Gabapentin is structurally related to the neurotransmitter GABA (gama-aminobutyric acid), but does not appear to effect GABA receptors or GABA activity at receptor sites. It also has been shown to lack interaction with numerous other central nervous system receptors. The pharmacological mechanism of its therapeutic actions remains unknown.[1]

Despite this pharmacological ambiguity, or possibly because of it, gabapentin has enjoyed a reputation as being a safe and effective medication for numerous clinical conditions. While its safety has not been officially questioned (routine laboratory monitoring is not required and significant drug-drug interactions are minimal[4]), its broad apparent efficacy has not held up under closer scrutiny.[2,3] However, clinical use has continued to increase and internationally was up about 1% in 2004 for a ranking of 15th in worldwide sales.[5]

Kansas Medicaid data indicates that from August 2003 through August 2005, the number of gabapentin claims increased by 18%. Of 4,315 patients with a claim for gabapentin in a recent 60 day time frame, over 60% had a submitted diagnosis that the current clinical literature does not support in terms of gabapentin efficacy.

Common Off-Label Uses: Clinical Evidence

Peripheral Neuropathy: The clinical literature in support of gabapentin use for conditions of neuropathic pain is the strongest of all the off-label uses. In addition to open-label and retrospective data, it includes three randomized, controlled trials with over 100 patients each. While questions remain regarding gabapentin's exact place in therapy relative to other accepted treatments, such as some antidepressants or carbamazepine, the benefits of gabapentin in neuropathic pain are fairly well established.[2,3,6]

Acute Pain: Studies investigating the analgesic effect of gabapentin postoperatively have yielded mixed results. Preoperative administration of gabapentin reduced postoperative ratings of pain and narcotic consumption in some, but not all studies.[7,8] Also, in some of the apparent positive studies adverse effects and outcomes were unchanged, therefore the value of decreased narcotic consumption is unclear.[9] A Cochrane Collaboration review concluded that there is currently "no logic in using gabapentin to manage acute nociceptive pain when there are other (effective) remedies".[3]

Trigeminal Neuralgia: Literature regarding the use of gabapentin in trigeminal neuralgia is limited to naturalistic data and case reports. In the absence of controlled study data, it is

impossible to accurately characterize its role. Therefore, use of gabapentin for trigeminal neuralgia is not currently recommended.[2,3]

Migraine: Gabapentin has controlled research data supporting its efficacy for migraine prophylaxis over placebo, but no direct comparative data exists versus more established, standard therapy.[2] One study of the costs of migraine therapy found that divalproex sodium was at least as effective and less expensive when compared with gabapentin. This study reported that divalproex patients would have to have more than 10 migraine episodes per month for it to be cost effective while gabapentin patients would have to have more than 24 episodes.[10] The American Academy of Neurology guidelines for headache management place divalproex, amitriptyline, timolol, and propranolol above gabapentin in their treatment hierarchy, with several nonsteroidal anti-inflammatory drugs, fluoxetine, and Vitamin B-12 on the same level as gabapentin.[11]

Bipolar Disorder: Initial optimistic results from case reports and open, naturalistic studies have generated substantial interest in gabapentin as a potential therapeutic agent in acute mania and bipolar disorder. However, this early optimism dissipated as actual controlled trials began to be reported in the literature.[2] In a study sponsored by Pfizer, the manufacturer of brand gabapentin (Neurontin®), the drug was found to be no better than placebo, for bi-polar disorder.[12] Current consensus is that gabapentin has no role in the management of bipolar disorder.[13,14]

Anxiety Disorders: Due in part to its sedative side effects, clinical utilization of gabapentin in various anxiety disorders has outpaced the investigation of its application for this use. As has been discussed in other areas, initial case reports and naturalistic studies were generally positive. However, controlled research remains limited at this point in time. Further investigation is needed before entertaining gabapentin as a first-line therapy for anxiety disorders. Additional information is also needed to clarify any potential role it may have as an augmenting agent in individuals who do not adequately respond to conventional therapy.[15,16]

Conclusions on the Use of Gabapentin

The list of potential uses for gabapentin reported in the literature continues to grow and includes attention-deficit/hyperactivity disorder (ADHD), restless legs syndrome, complex regional pain syndrome (previously known as reflex sympathetic dystrophy), and multiple sclerosis. However, the discussion on clinical data and utilization would basically be a repeat of the above for anxiety disorders. Initial data from case reports and naturalistic studies appear positive, but more controlled research is needed before a definitive place in therapy can be recommended in any of these areas.[2]

The Kansas Drug Utilization Review Board (KDURB) has recently made a recommendation to the Kansas Medical Assistance Program (KMAP) to limit the use of gabapentin based in part on two recent reports. These reports, Drug Class Review on Antiepileptic Drugs in Bipolar Mood Disorder and Neuropathic Pain (2004) by The Evidence-based Practice Center[17] and Guidance on the Use of Gabapentin by the Veterans Health Administration[18] parallel the information contained in this newsletter and support the indications listed in Table 2 below. Based on the KDURB recommendation, KMAP has approved a new policy that requires patients to have one of the diagnoses indicated in Table 2 in order to receive gabapentin under the program. These limitations have also been extended to the more recently marketed, but related agent, Lyrica® (pregabalin). Available information about off-label use of Lyrica® (pregabalin) is much more limited than that for gabapentin. This policy, which was implemented January 10, 2006, requires clinicians to communicate the intended use of gabapentin or pregabalin to the dispensing pharmacist. It is recommended the physician indicate the diagnosis on the prescription, but verbal clairification may be necessary in some instances. Pharmacists are required to enter the appropriate ICD-9 code (see Table 2) on the claim. In addition, pregabalin will be restricted to patients 18 years of age or older, 3 units per day, and 600 mg per day as recommended by the KDURB in November 2005. Information about this policy has been published in a provider bulletin that was distributed prior to the implementation date of January 10, 2006.

Table 2: Gabapentin (Neurontin®) Indications [ICD-9 Codes]

FDA-Approved Indications:	Off-Label Indications Deemed Appropriate by the Kansas Drug Utilization Review Board:
• Partial Seizures with or without generalization • Postherpetic Neuralgia	• Other Seizure Types [345.0 through 345.9, 780.39, 907.0] • Neuropathic Pain [356.9]

Gabapentin - cont.

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